BASIC RESEARCH

Breakable stent for interventions in infants and neonates: an animal study and histopathological findings

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Objective: To test in a neonatal animal model the feasibility and biocompatibility of a new breakable stent that can be broken open by balloon dilatation during reintervention for use in neonates and infants.
Materials and methods: Medical grade stainless steel breakable stents (n = 16) were interventionally implanted in systemic arteries in neonatal piglets (n = 7). Patency of the stented segments was shown by repeated angiography. Stents were redilated up to three times. After a follow up of 18–165 days the animals were killed and the tissue block containing the stent was excised. Besides standard histological examination, scanning electron microscopy was used for biocompatibility screening.
Results: The stents were broken by redilatation with a conventional angioplasty balloon catheter. During follow up, patency of all stented segments was shown angiographically. One stent became dislocated during implantation. One vessel ruptured during redilatation when an inadequately large balloon catheter was used for dilatation. No other complications were observed. Scanning electron microscopy showed complete cellular coverage of the stent struts. Histological examination showed thinning of the vessel wall and partial rupture of the media at the site of stent breakage. An only mild inflammatory reaction was detected.
Conclusion: The new breakable stent can be broken open by simple angioplasty. Feasibility, effectiveness, and biocompatibility were shown in an animal model. Surgery to remove stents from paediatric patients due to disproportion between a previously implanted stent and the growing vessel may be avoided by the use of a breakable stent.

The use of interventionally implanted stents for treatment of vascular stenosis in children was first reported in 1991.[1] Stenting has since become a standard procedure for several indications. A major problem of using stents in small children is that the circumferential size of the stent does not adapt to the growth of the stented vessel segment.[2] This problem has in part been overcome by repeated stent dilatations.[3–5] However, redilatation is also limited by the restricted maximum stent diameters, especially when coronary stents are implanted in infants or neonates.

Modifying a concept of Mullins and co-workers (to the best of our knowledge not published yet; CE Mullins 2001, personal communication), we therefore developed a breakable stent suitable for application in neonates that can remain permanently in the treated vessel. The breakable stent is longitudinally open and reconnected by surgical sutures (fig 1). These sutures serve as predetermined breaking points during redilatation.

In this study we tested feasibility and biocompatibility of the new breakable stent in a neonatal animal model.

METHODS

Animal studies

The animal experiments were conducted according to the guidelines of the German Animal Protection Law and were approved by the state agency supervising animal experimentation. All interventions were performed as sterile procedures under general anaesthesia. Except for aspirin 2 mg/kg daily and sedative and analgesic agents during interventions, no other medications were administered. All animals were healthy showing no signs of systemic disease.

Intervention and devices

Stents were implanted percutaneously through an introduction sheath in the femoral artery. The stents were manually mounted on a 6 mm valvoplasty catheter (Dr Osypka GmbH, Rheinfelden, Germany) and positioned in non-stenotic arterial vessels. Interventions were repeated to show patency angiographically. For redilatation according to the animals' growth, conventional angioplasty catheters (Powerflex or OPTA; Cordis, Warren, New Jersey, USA) were used.

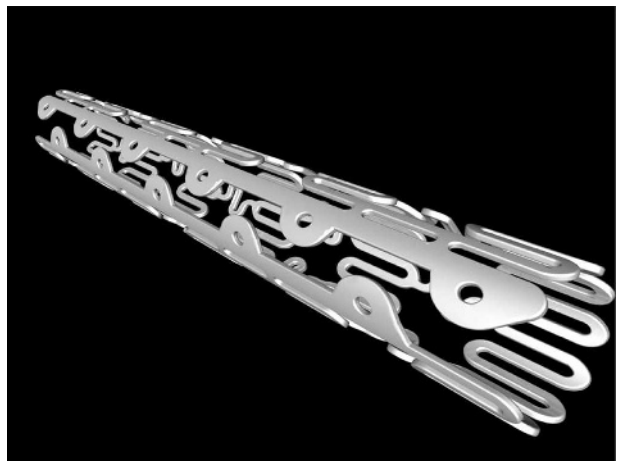

Figure 1 The breakable stent. The stent is longitudinally open. For implantation, the neighbouring eyelets are connected by means of surgical sutures.

The breakable stent (Dr Osypka GmbH) is made from medical grade stainless steel (316 L) with gold coating. The five stents in the pilot study were made from 316 L steel without gold coating. The breakable stent has a standard coronary stent design. In contrast to regular coronary stents, the breakable stent is cut open longitudinally and reconnected by the use of surgical sutures (Prolene 6-0, Ethicon GmbH, Norderstedt, Germany).

Preparation

Immediately after the animal's death, the tissue blocks containing the stents were removed. After being flushed with normal saline, the specimens were fixed in formalin. The formalin fixed specimen were embedded in methylmethacrylate (Technovit 9100; Kulzer & Co, Wehrheim, Germany), hardened at −3℃, and subsequently sectioned in slices of 0.3 mm with a diamond cutter (Exakt Apparatebau GmbH, Norderstedt, Germany). These slices were ground down to 10–20 μm with a rotational grinding machine (Exakt Apparatebau GmbH). Slices were stained with Richardson blue. One portion of the tissue block was submitted for scanning electron microscopy and placed in glutaraldehyde (3%). After being washed and dehydrated through an ascending ethanol series, the specimens were dried in a critical point dryer and sputter coated with gold.

RESULTS

Stent implantation

In a pilot study five stents were implanted in two piglets. One of the five stents became dislocated immediately after initial implantation into the descending aorta. In this case, the balloon diameter was obviously not sufficient relative to the unobstructed vessel. In addition visibility of these stents under fluoroscopy was inadequate. To solve this problem, manufacturing of stents for the long term study was modified by an additional gold coating.

In the long term animal study, 11 gold coated stents were implanted in five piglets (table 1). Age at implantation ranged from 20–138 days with a mean of 42 days; weight ranged from 6–40 kg with a mean of 12 kg. Stents with an initial diameter of 6 mm were implanted in unobstructed vessels of 5 mm as measured by angiography. No stents were dislocated during introduction or implantation of the stents in the long term animal study.

Reinterventions

Repeated control angiographies showed patency of all stented vessel segments during follow up. Stents were redilated one to three times after intervals of two to four weeks to adopt stent size to growth of the vessel. For redilatation of the stent a balloon catheter was used with a size of up to 125% of the vessel diameter as measured by angiography. Stents were broken by balloon dilatation in seven of seven attempts with an 8 or 9 mm angioplasty catheter (fig 2). The remaining four stents were exclusively redilated up to a size of 7 mm with no intended breaking of the stent.

The pigs were killed with an overdose of barbiturate between 18 and 165 days after implantation of the stents.

As a complication in the long term animal study, one vessel ruptured during redilatation of a breakable stent when an inadequately large balloon catheter was used with a diameter of 180% of the stented vessel segment. Control angiography in this animal showed contrast media in the perivascular region. The animal died because of loss of blood.

Pathological examination

Gross examination showed complete expansion of all stents with all stent struts being in contact with the vessel wall. The stents were lined by a thin and transparent layer of smooth

Table 1 Data on the long term animal study

Animal	Site of implantation	No of redilatations	Broken open	Age at implantation (days)	Age at explantation (days)	Time from implantation to explantation (days)	Weight at implantation (kg)	Weight at explantation (kg)	Weight gain from implantation to explantation	Complications
1	Aorta abdominalis	1	No	26	188	162	8	53	563%	None
1	Brachiocephalic artery	2	Yes	26	188	162	8	53	563%	None
2	Subclavian artery	2	Yes	28	193	165	7	75	971%	None
2	Brachiocephalic artery	1	No	138	193	55	40	75	88%	None
3	Brachiocephalic artery	3	Yes	35	145	110	10	65	550%	None
3	Carotid artery	2	Yes	35	145	110	10	65	550%	None
4	Brachiocephalic artery	2	Yes	27	94	67	6	25	317%	Vessel rupture
4	Aorta abdominalis	1	Yes	27	94	67	6	25	317%	None
4	Carotid artery	1	No	76	94	18	20	25	25%	None
5	Brachiocephalic artery	3	Yes	20	88	68	7	28	300%	None
5	Carotid artery	1	No	20	88	68	7	28	300%	None
Minimum		1		20	88	18	6	25	25%	
Maximum		3		138	193	165	40	75	971%	
Mean		2		42	137	96	12	47	413%	

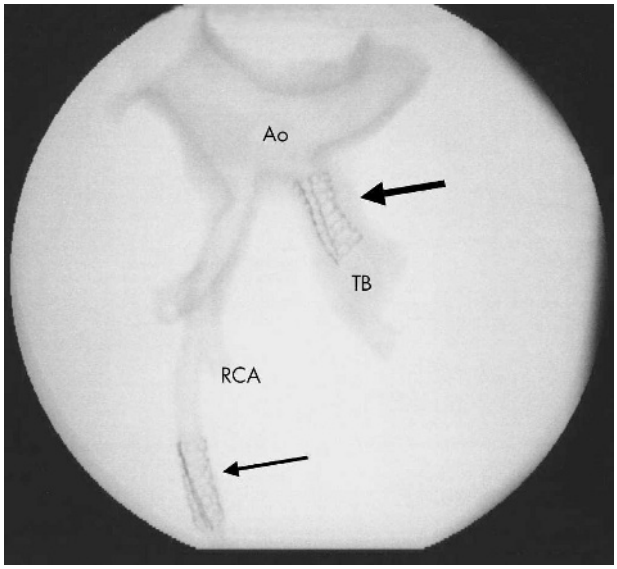

Figure 2 Angiography of the pathological specimen of animal 5 after explantation of one stent in the brachiocephalic artery (broken open; bold arrow) and one stent in the right carotid artery (intact; light arrow). Ao, aorta; TB, brachiocephalic artery; RCA, right carotid artery.

tissue. Subendothelial or adventitial haemorrhage was not seen macroscopically.

Scanning electron microscopy showed complete cellular coverage of the stent struts (fig 3). No metal or suture material was detected in direct contact with the blood stream. No thrombus had formed at the vascular surface in any of the specimens.

Histological analysis showed neointima formation in the stented vessel segments, which was shown to be pronounced around the stent struts (fig 4). The thickness of the neointima varied between the specimens and within one specimen it varied in an unpredictable pattern. Maximum neointima thickness in our series was 115 μm in a specimen with a stent implantation time of 162 days. Some media compression beneath the stent struts was seen.

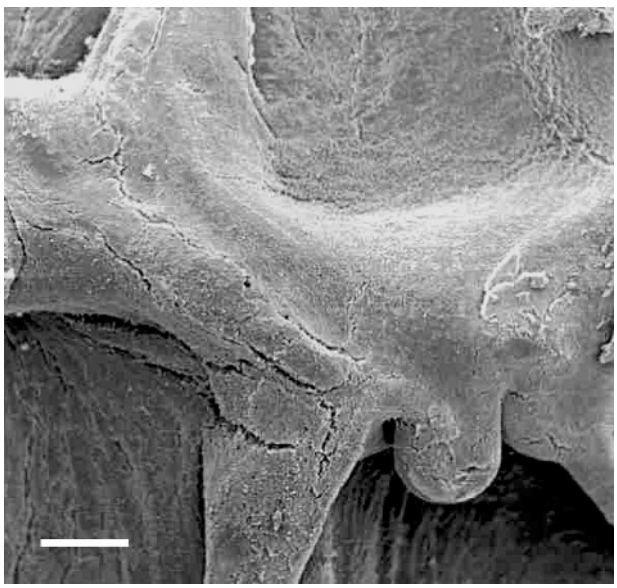

Figure 3 Electron microscopic view of the inner vascular surface of the brachiocephalic artery with the stent struts covered by endothelium 55 days after implantation (animal 2). Scale bar = 200 μm.

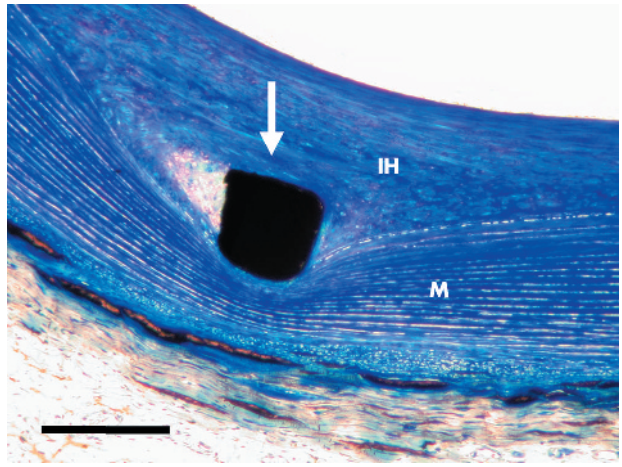

Figure 4 Histological view of the carotid artery vessel wall 68 days after implantation of a breakable stent showing mild intimal hyperplasia (IH) (animal 5). The white arrow indicates a stent strut. M, media. Richardson staining. Scale bar = 100 μm.

At the site of stent breakage, thinning of the vessel wall and partial dissection of the media but not of the adventitia were seen histologically. In one specimen the free edge of the stent had bent after breaking (fig 5). There was no evidence of medial or adventitial haemorrhage. A mild inflammatory reaction was detected with single mononuclear cells locally related to the stent struts. No dense inflammatory infiltrates or foreign body reactions were seen.

DISCUSSION

In 1992, Rosenthal and Qureshi[2] stated that stent implantation should be restricted to vessels that have attained their final size or have nearly done so. Concern was raised that stents of a fixed diameter in growing vessels would eventually become rigid stenoses with consecutively reduced flow.

Redilatation of the stented vessel segment was introduced to adapt the stent size to the growth of the patient[1] and was shown to be an effective and safe method.[3–6] Indeed, patients' growth was identified as the most common indication for

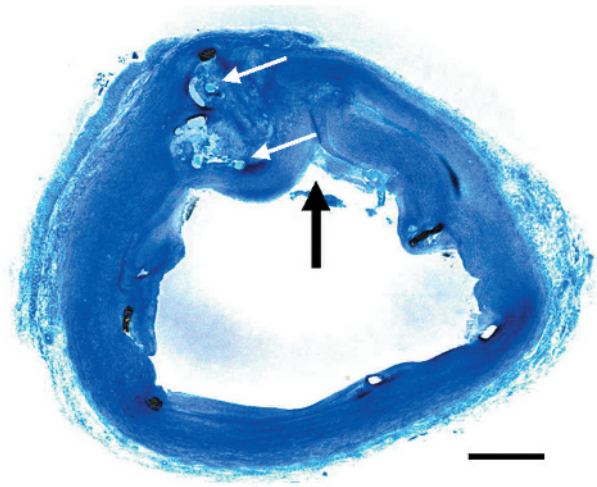

Figure 5 Histological view of a cross section of a brachiocephalic artery with an implanted breakable stent 110 days after implantation and 12 days after breaking (animal 3). The bold arrow indicates partial rupture of the vessel wall. Small white arrows indicate residual suture fragments. Richardson staining. Scale bar = 1 mm.

redilatation of stented pulmonary arteries, whereas external compression and intimal hyperplasia less often led to reintervention.[7] Redilatation is also limited by restricted maximum stent diameters.

Hatai *et al*[5] reported on the follow up of 26 children under 1 year of age who had received one or more stents. After a follow up of up to 36 months (median 12 months), 11 of these patients had successful redilatations within a median of 10 months after implantation; in 10 patients stents were surgically removed or augmented by implantation of a patch after the stented vessel was cut longitudinally. They summarised that the rate of surgical interventions after stent implantation in infancy increases significantly with an increasing follow up interval. Nevertheless, the use of stents in combination with redilatation during follow up may at least postpone surgical intervention.

Our group previously published a different approach to the problem of mismatch of maximum stent diameter and vessel growth.[8] The concept of the ''babystent'' was not pursued further because of limited radial stent stability after redilatation.

The concept of a breakable stent aims at a solution to the problem of limited adaptation of stents to vessel growth in young patients. The breakable stent can be implanted with a diameter of 5–6 mm. This is sufficient for an interventional approach to neonatal coarctation of the aorta. An introduction sheath of 4 or 5 French is needed for implantation, thus making the stent applicable to neonates. During follow up, the stent can be redilated to adopt the stent size to the growing vessel. When a diameter of 8–9 mm is achieved and vessel growth requires further enlargement, the stent can be broken open by simple redilatation with the longitudinally applied sutures serving as predetermined breaking points. Thus, the breakable stent is not limited by a maximum diameter. If needed, at this point, a larger regular peripheral stent may be implanted that has enough potential for adoption to vessel growth until adulthood.

Conclusions

In this study we showed the feasibility, effectiveness, and biocompatibility of the breakable stent in an animal model. The concept of a breakable stent combines advantages of stents of different sizes. The breakable stent requires only a small introduction sheath. It may be redilated without the limit of a maximum diameter of a regular coronary stent, since it can be broken open by means of simple angioplasty if enlargement to a diameter of more than 8–9 mm is required. In our study, the rapid body growth of the piglets served as a valuable model for the successful adoption of the breakable stent to vessel growth.

Histopathological analysis of the stents showed good biocompatibility of the device with complete cellular coverage of the stents struts, with mild intimal hyperplasia after stent implantation and a mild inflammatory reaction in the surrounding tissue. At the site of stent breakage, thinning of the vessel wall with partial rupture of the media was observed. The vessel did not rupture when a balloon catheter of adequate size was used for redilatation.

With the concept of the breakable stent, surgery because of mismatch of stent size and vessel growth during development may be avoided or at least postponed.

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We declare not to have any competing interests in accordance with the BMJ declaration.

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